JCI The Journal of Clinical Investigation

Maternal-fetal conflict — lessons from a transgene

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J Clin Invest. 2002;110(3):307-309. https://doi.org/10.1172/JCI16389.

Commentary

Fetal growth is a complex process that depends on the genetic makeup of the fetus, the success of the implantation process, the availability of nutrients and oxygen to the fetus, intrauterine insults (e.g., hypoxia, cigarette smoking, infection), maternal nutrition, and a variety of growth factors, cytokines, and proteins of maternal and fetal/placental origin (see refs. 1, 2 for reviews). In the maternal circulation and decidua and in the fetus, IGFs and their binding proteins (IGFBPs) and receptors are important regulators of fetal growth. The question of whether the mother or the fetus ultimately controls fetal growth and placentation has been complicated by the finding that IGFBP-1 is produced by both maternal and fetal tissues. In this issue of the JCI, Crossey et al. (3) investigate this maternal-fetal conflict by targeting over-expression of human IGFBP-1 to the mouse decidua and/or the fetus. While providing new insights as to who is in control during fetal development, these authors raise new questions about mechanisms governing fetal and placental growth and placentation. Homologous recombination studies in mice have demonstrated the importance of IGF-I and IGF-II in fetal and placental growth, respectively. Igf-1–/– pups exhibit a 40% reduction in birth weight (4). Mice lacking the type II IGF receptor, which contributes to IGF-II turnover but is not essential for transducing signals from IGF-II, exhibit a […]

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See related article, pages 411–418.

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J. Clin. Invest. **110**:307–309 (2002). doi:10.1172/JCI200216389.

Fetal growth is a complex process that depends on the genetic makeup of the fetus, the success of the implantation process, the availability of nutrients and oxygen to the fetus, intrauterine insults (e.g., hypoxia, cigarette smoking, infection), maternal nutrition, and a variety of growth factors, cytokines, and proteins of maternal and fetal/placental origin (see refs. 1, 2 for reviews). In the maternal circulation and decidua and in the fetus, IGFs and their binding proteins (IGFBPs) and receptors are important regulators of fetal growth. The question of whether the mother or the fetus ultimately controls fetal growth and placentation has been complicated by the finding that IGFBP-1 is produced by both maternal and fetal tissues. In this issue of the *JCI*, Crossey et al. (3) investigate this maternal-fetal conflict by targeting over-expression of human IGFBP-1 to the mouse decidua and/or the fetus. While providing new insights as to who is in control during fetal development, these authors raise new questions about mechanisms governing fetal and placental growth and placentation.

Homologous recombination studies in mice have demonstrated the importance of IGF-I and IGF-II in fetal and placental growth, respectively. *Igf-1*$^{-/-}$ pups exhibit a 40% reduction in birth weight (4). Mice lacking the type II IGF receptor, which contributes to IGF-II turnover but is not essential for transducing signals from IGF-II, exhibit a 25% increase in placental mass (5), whereas animals null for the type I (signaling) IGF receptor demonstrate severe fetal growth restriction (3). In humans, a natural deletion of exons 4 and 5 of the *IGF-1* gene results in severe pre- and post-natal growth restriction and mental retardation (6). Furthermore, IGF-I concentrations in full-term human cord blood correlate with fetal birthweight (7–11). Together, these data underscore the importance of IGF-I in human fetal growth and development.

Regulation of IGF bioavailability is tightly controlled by IGF binding proteins, a family of high-affinity proteins in the circulation, synthesized locally in tissues that are mostly inhibitory to IGF actions and that have IGF-independent actions. The literature supports a major role for elevated IGFBP-1 in the fetus in inhibiting fetal growth (12, 13), probably by sequestering fetus-derived IGF-I. IGFBP-1 concentrations in fetal blood collected by cordocentesis in the third trimester are significantly higher in growth-restricted babies than in normal-weight babies (9, 10, 13). In contrast to the positive correlation between fetal serum IGF-I and birthweight, IGFBP-1 concentrations are *inversely* correlated with birthweight (9, 10, 13). On the maternal side, IGFBP-1 is a major product of the maternal decidua and is believed to inhibit (14) or enhance (15) trophoblast invasion into the maternal decidua, which can affect normal placental development and thus fetal growth.

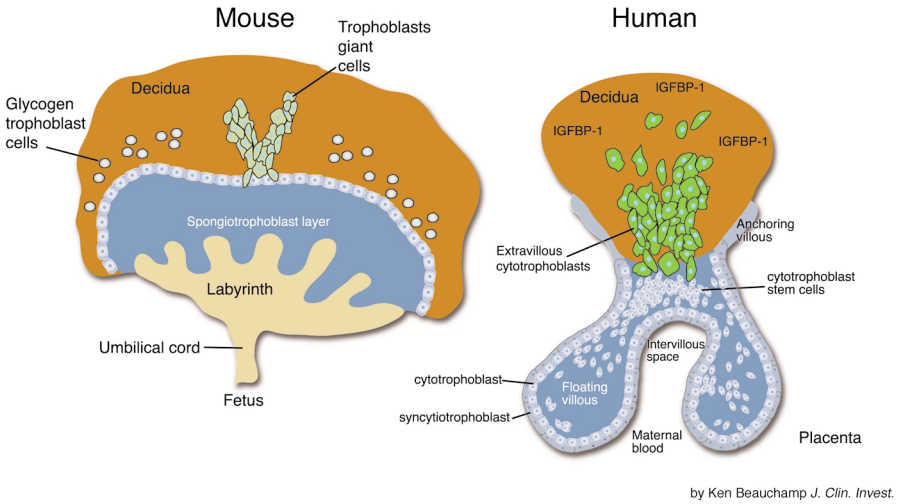

Figure 1
Schematic of events occurring at the decidual/trophoblast interface, comparing mouse (left) and human (right). In the mouse, the decidua, which does not normally express IGFBP-1, and the layers of the placenta are shown. In the human decidua, IGFBP-1 is normally expressed in high abundance and is positioned to regulate extravillous trophoblast invasion into this compartment (see text).

Crossey et al. (3) have now addressed the effects of IGFBP-1 of fetal and/or maternal (decidual) origin on the regulation of fetal growth and placentation, using a mouse model. They find that overexpression of human IGFBP-1 in the mouse fetus is associated with transient and modest fetal growth restriction, as judged by decreased fetal weight and increased placental/fetal weight ratio, but no change in crown rump length. This effect is evident at embryonic day 11 but is followed by catch-up growth by embryonic day 17.5. These observations, which are similar to those of Rajkumar et al. in another IGFBP-1 transgenic mouse line (16), raise the question of why fetal growth restriction does not continue throughout the pregnancy. Perhaps a compensatory increase in IGF-I production improves the fetus' access to nutrition and supports fetal growth even in the face of high IGFBP-1 levels — a possibility that could be tested by measuring total and free circulating IGF-I throughout gestation. Moreover, while IGFBP-1 regulates minute-to-minute bioavailability of IGF-I (17, 18), the ligand blots in the manuscript by Crossey et al. indicate that another IGFBP, IGFBP-3, is the major IGFBP in fetal serum. Perhaps a compensatory increase in free IGF-I by proteolysis of IGFBP-3 in fetal circulation can lead to an increase in bioavailable IGF-I or to posttranslational modification that might reduce the affinity of IGFBP-1 for IGF-I. Either of these mechanisms could enable the IGFBP-1 transgenic fetuses to achieve normal weight at the time of delivery. Alternatively, the fetus may be intrinsically more or less sensitive to the effects of growth factor restrictions or similar insults at different stages, perhaps because redundant compensatory mechanisms come into play later in gestation. It is reasonable, however, that modest fetal growth restriction would be observed in fetal IGFBP-1 transgenic models, as opposed to the severe growth restriction observed in animals deficient for IGF-I or the type I IGF receptor (4), since some IGF must still be in the circulation.

Complex interactions between the invading trophoblast and the maternal decidual and vascular endothelial cells occur at the maternal-placental interface (Figure 1). In humans, IGFBP-1, a major product of the maternal decidua, is well positioned to regulate the IGF-II–expressing trophoblast as it migrates through the decidua to reach the maternal vasculature (19). Two key observations in the present report underscore the importance of maternal IGFBP-1 by showing, first, that amniotic fluid IGFBP-1 is almost certainly of decidual origin, and, second, that this IGFBP-1 is crucial for normal regulation of decidual and placental development, as well as trophoblast differentiation and invasion. The observation that the decidual zone in transgenic females is markedly reduced compared to that in wild-type females suggests that IGFBP-1 in the decidua may inhibit IGF-dependent growth and differentiation of this tissue or may directly affect these processes, independent of IGFs. Placentae from F^+/M^- matings also show evidence of aberrant trophoblast differentiation, suggesting that IGFs are important in this process. While the decidual zone is smaller in the IGFBP-1 transgenics, the junctional zone is larger, with a higher ratio of spongiotrophoblasts to glycogen cells, and the labyrinthine zone (where nutrient and oxygen transfer primarily occur to the fetal circulation) is markedly increased (Figure 1). A recent report on the effects of deletion from the *Igf-2* gene of a transcript (PO) that is specifically expressed in the labyrinthine trophoblast (20) offers some insight into the effects observed in the IGFBP-1 transgenic animal model. Loss of Igf-2 (PO) expression in the labyrinthine trophoblast results in decreased placental growth, decreased passive permeability to nutrient transport, and subsequent up-regulation of active amino acid uptake. However, this compensatory mechanism ultimately fails in these fetuses, leading to fetal growth restriction. In the IGFBP-1 transgenic model, the labyrinthine layer is increased and fetal growth restriction is observed early in gestation with catch-up growth later in gestation in wild-type fetuses, but with continued restricted growth in transgenic fetuses. IGFBP-1 over-expressed in the decidua may inhibit giant trophoblast invasion into the decidua early in gestation, limiting access to the maternal circulation. If decidual-derived IGFBP-1 does not diffuse well into the labyrinthine layer to inhibit endogenous IGF-II action, an IGF-dependent compensatory process may then develop to increase nutrient transfer to the fetus and restore normal fetal growth, although Crossey et al. did not find an increase in IGF-II mRNA globally in the placenta. Alternatively, the compensatory process could be independent of IGFs. In the IGFBP-1 transgenic fetus, a "second hit" of decreased IGF bioavailability could result in persistent fetal growth restriction. In both instances, fetal growth restriction would not be expected to be as severe as in targeted deletions of IGFs.

Although different mechanisms governing stromal decidualization and trophoblast invasion may operate at the decidual/trophoblast interface in mice and humans, limited trophoblast invasion with subsequent fetal growth restriction observed herein is reminiscent of the clinical disorder of preeclampsia and in utero hypoxia, and indeed the IGF system is important in this pregnancy-specific disease (21). Human intrauterine growth restriction (IUGR) is another serious complication of pregnancy, leading to an increased risk of perinatal hypoxia, preterm delivery, and fetal demise. It is increasingly evident that the foundations of lifelong health are built in utero, and recent studies show that long-term health risks continue for infants surviving IUGR, including increased risks of hypertension (22, 23), dyslipidemia, obesity, diabetes, precocious adrenarche and infertility (24). The model described by Crossey et al. (3) holds great promise for determining the underlying causes of fetal growth restriction due to uteroplacental insufficiency, as it involves the IGF system. What a system for conflict resolution!

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